

REMARKS

Prior to this Amendment, Claims 11-23 were pending. Claims 11-20 and 22-23 were under active consideration, and Claim 22 was withdrawn. Of the Claims under consideration, Claims 11-23 have been canceled to expedite prosecution and secure allowance of this application, without prejudice to Applicants' rights to prosecute the subject matter of the canceled claims in one or more related applications.

With this amendment, Claims 24-35 are new. Claims 24-34 are pending and Claim 35 is withdrawn.

Amendments of the Drawings

As shown in the Marked up Copy of Figure 1A, the amino acid sequence of the VH region of HuAIP13 has been amended to correct the typographical errors in the VH chain region of HuAIP13. Figure 1A has been amended to show that the amino acid Ile is located at position 55 and the amino acid Thr is located at position 59 in CDR2 of the HuAIP13 VH chain region.

Support for this amendment can be found in SEQ ID NOs: 6 and 3. SEQ ID NO: 6 depicts the amino acid sequence for the AIP13 CDR2 VH chain region (see also page 10, lines 31-33 of the specification) and SEQ ID NO: 3 depicts the amino acid sequence for the AIP13 VH chain region (see also page 10, lines 27-29). Further support for this amendment can be found in Example 5, which describes the humanization of the murine AIP13 antibody. As described in Example 5, page 28, lines 7-9, humanization of the murine antibody involved grafting the murine CDR sequences (SEQ ID NOs: 5, 6, 7, 8, 9 and 10; see also page 10, line 31 through page 11, line 2 of the specification) in to the selected human framework sequences. Thus, as set forth in SEQ ID. NO: 6, the specification at page 10, line 32, and the marked up copy of Figure 1A, the amino acid sequence for CDR2 VH of HuAIP13 is WINTIGEPTYADDFKG.

As shown in the Marked up Copy of Figure 1A, the amino acid sequence of the VH region of T55I has been amended to correct the typographical errors in the VH chain region of T55I. Figure 1A has been amended to show that the amino acid Ile is located at position 55 and the amino acid Thr is located at position 59 in CDR2 of the T55I VH chain region.

Support for this amendment can be found in Example 8 of the application as filed. As described in Example 8, beginning on page 45, line 8 through page 46, line 20, alignment of the VH chain regions of HuAIP12 and HuAIP13 revealed that there were only two amino acid differences between the VH chain regions, i.e., at positions 55 and 104. Mix and match analysis of the heavy and light chains between HuAIP12 and HuAIP13 indicated that the HuAIP12 VH region was important for high affinity binding to human IP-10. Because the HuAIP12 and HuAIP13 variable heavy regions differed at only two positions, position 55 and position 104, each of these positions was replaced with the corresponding residue from the HuAIP13 VH region (see Example 8, page 46, lines 11-14). As described on page 46, lines 14-20, the HuAIP12 VH variant designated T55I was generated using site directed mutagenesis to make a substitution from Thr to Ile at position 55 in the HuAIP12 VH region. As discussed on page 47, lines 1-14, the replacement of Ile with Thr at position 55 in the VH region of HuAIP12 unexpectedly increased the affinity of HuAIP12 to human IP-10, suggesting that the Thr residue at position 55 negatively influenced the binding affinity of HuAIP12 to IP-10.

Additional support that the T55I CDR2 VH amino acid sequence is WINTEIGEPTYADDFKG can be found in an Abstract entitled "Generation of a High Affinity Humanized Anti-IP-10 Monoclonal Antibody by Protein Engineering" (Pandya, Deepal et al. "Generation of a High Affinity Humanized Anti-IP-10 Monoclonal Antibody by Protein Engineering." 2005. Retrieved August 3, 2009 from the Midwinter Conference of Immunologists website: http://www.midwconfimmunol.org/element/filemgr_repository/Pandya.pdf; attached hereto as Exhibit A). The Abstract describes the mix and match analysis of HUAIP12 and HuAIP13 to determine the amino acid residues essential for high affinity binding to human IP-

10. The Abstract corroborates that the T55I variant was made by substituting the Thr with Ile at position 55 in CDR2.

Applicant also provides a copy of the Poster that was presented at the 2005 Midwinter Conference of Immunologists (attached hereto as Exhibit B). Figure 2 of the Poster provides the amino acid sequence of the VH chain for HuAIP13. As shown in Figure 2 of the Poster, position 55 in the VH chain of HuAIP13 is Ile.

No new matter is added by virtue of the amendment to Figure 1A.

Amendments of the Specification

The specification has been amended, where appropriate, to refer to the mature heavy and light chains of HuAIP12 and HuAIP13. Specifically, references to amino acid sequences containing the signal peptides have been replaced with references to the mature amino acid sequences in the specification to clarify that antibodies for use in the invention are the mature antibodies, and not unprocessed antibodies containing a signal sequence. See, for example, Example 6, page 40, line 29 through page 42, line 2, describing the expression of the mature HuAIP12 antibody from mini-exons including signal peptides.

Accordingly, references to the unprocessed antibodies have been replaced with references to the mature antibodies in the "Summary of the Invention", the "Brief Description of the Drawings", and in the specification at pages 10, 15, and 44 as follows:

SEQ ID NO: 50, which provides the amino acid sequence for the unprocessed HuAIP12 VH region has been replaced with SEQ ID NO: 45, which provides the amino acid sequence for the mature HuAIP12 VH region;

SEQ ID NO: 48, which provides the amino acid sequence for the unprocessed HuAIP12 VL region has been replaced with SEQ ID NO: 46, which provides the amino acid sequence for the mature HuAIP12 VL region;

SEQ ID NO: 20, which provides the amino acid sequence for the unprocessed HuAIP13 VH region has been replaced with SEQ ID NO: 13, which provides the amino acid sequence for the mature HuAIP13 VH region;

SEQ ID NO: 18, which provides the amino acid sequence for the unprocessed HuAIP13 VL region has been replaced with SEQ ID NO: 15, which provides the amino acid sequence for the mature HuAIP13 VL region.

Lines 19-21 on page 11 of the specification describe a mature light chain variable region sharing sequence identity with SEQ ID NO:4 (i.e., murine AIP13 VL chain) and SEQ ID NO: 14. SEQ ID NO: 14 is the amino acid sequence for the VH segment DP-3 and the J segment JH6. To correct this typographical error, SEQ ID. NO: 14 has been replaced with SEQ ID NO: 15, which is the mature VL chain of HuAIP13.

Lines 28-32 on page 15 of the specification recite SEQ ID NOs. for the amino acid sequences of the HuAIP13 heavy chain variable (i.e., SEQ ID NO: 13) and light chain variable (SEQ ID NO: 14) regions. SEQ ID NO: 14 is the amino acid sequence for the VH segment DP-3 and the J segment JH6. To correct this typographical error, SEQ ID. NO: 14 has been replaced with SEQ ID NO: 15, which is the mature VL chain of HuAIP13.

Lines 31-32 on page 44 of the specification recite SEQ ID NO: 17 as the VH chain amino acid sequence and SEQ ID NO: 18 as the VL chain amino acid sequence of HuAIP13. SEQ ID NO: 17 is the nucleotide sequence for the HuAIP13 VL chain. To correct this typographical error, SEQ ID. NO: 17 has been replaced with SEQ ID NO: 13, which is the amino acid sequence of the VH chain for HuAIP13. SEQ ID NO: 18 is the unprocessed VL chain amino acid sequence for HuAIP13. To correct this typographical error, SEQ ID NO: 18 has been replaced with SEQ ID NO. 15, which is the mature VL chain amino acid sequence for HuAIP13.

No new matter is introduced by virtue of the amendments made herein to the specification.

Amendments of the Claims

Claims 11- 23 have been cancelled and replaced with new claims 24-35 which are directed to an isolated anti-IP-10 antibody or antigen binding fragment which binds to a protein encoded by SEQ ID NO: 1, (i.e., human IP-10) and comprises, at a minimum, the heavy chain CDRs of SEQ ID NO: 78 (i.e., SEQ ID NOs: 5, 6, and 74) and the light chain CDRs of SEQ ID NO: 46 (i.e., SEQ ID NOs: 75, 76, and 77). Support for this amendment is described above and throughout the specification, see for example, page 8, line 31 through page 9, line 6; page 17, lines 6-9, Figure 1A and 1B, and the sequence listing as filed.

Claims corresponding to claims 11-13 and 16-22 have been reintroduced as new claims 27-29 and 30-35.

No new matter is introduced by virtue of the amendments made herein to the claims.

Replacement Sequence Listing

SEQ ID NO: 20, has been amended to correct the typographical error in the sequence. Specifically, the amino acid serine has been added at positions 137 and 138. Support for this amendment can be found in SEQ ID NO: 13.

SEQ ID NO: 78 has been amended to correct the typographical error in the sequence. Specifically, the amino acid amino acid Ile is located at position 55 and the amino acid Thr is located at position 59. Support for this amendment is discussed above.

No new matter is introduced by virtue of the amendments made herein to the Sequence Listing.

Rejection Under 35 U.S.C. § 112, second paragraph

Claim 23 is rejected under 35 U.S.C. § 112 as being indefinite. Claim 23 is cancelled, thus the rejection is moot.

Rejection Under 35 U.S.C. § 112, first paragraph

Claims 11-20, 22, and 23 are rejected for lack of enablement on the basis that the specification enables only (1) an antibody or fragment thereof wherein said antibody or antibody fragment comprises the variable heavy chain amino acid sequence of SEQ ID NO: 78 and the variable light chain amino acid sequence of SEQ ID NO: 46 (identical to SEQ ID NO: 48, except that SEQ ID NO: 46 lacks the signal peptide of SEQ ID NO: 48), and wherein said antibody or fragment thereof binds to the chemokine IP-10; and, (2) methods of using said antibody or fragment thereof to reduce the severity of at least on symptom of IBD.

Applicant has cancelled Claims 11-20, 22, and 23, rendering the rejection moot. Insofar as the rejection applies to newly added claims, the rejection is addressed below.

Claims 24-35 are directed to an isolated anti-IP-10 antibody or antigen binding fragment which binds to a protein encoded by SEQ ID NO: 1, (i.e., human IP-10) and comprise, at a minimum, the heavy chain CDRs of SEQ ID NO: 78 (i.e., SEQ ID NOS: 5, 6, and 74) and the light chain CDRs of SEQ ID NO: 46 (i.e., SEQ ID NOS: 75, 76, and 77).

Accordingly, the rejection under 35 U.S.C. § 112, first paragraph, for lack of enablement, has been obviated and should be withdrawn.

Rejections Under 35 U.S.C. § 102

Claims 11-13, 16, and 22 are rejected under 35 U.S.C. § 102(b) as being anticipated by Carosella et al., U.S. Patent No. 4,719,107. According to the Examiner, the antibody fragments of Carosella and the claimed antibody fragments are structurally identical.

Applicant has cancelled Claims 11-13, 16, and 22, rendering the rejection moot. Insofar as the rejection applies to newly added claims, the rejection is addressed below.

“A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference.” *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987).

Claims 24-35 are directed to an isolated anti-IP-10 antibody or antigen binding fragment which binds to a protein encoded by SEQ ID NO: 1, (i.e., human IP-10) and comprise, at a minimum, the heavy chain CDRs of SEQ ID NO: 78 (i.e., SEQ ID NOS: 5, 6, and 74) and the light chain CDRs of SEQ ID NO: 46 (i.e., SEQ ID NOS: 75, 76, and 77).

Carosella et al. teach the use of Fc fragments of human IgG for the treatment of autoimmune diseases. Carosella et al. do not teach the use of Fc fragments that bind to a protein encoded by SEQ ID NO: 1, and comprise the heavy chain CDRs of SEQ ID NO: 78 (i.e., SEQ ID NOS: 5, 6, and 74) and the light chain CDRs of SEQ ID NO: 46 (i.e., SEQ ID NOS: 75, 76, and 77).

Accordingly, the rejection under 35 U.S.C. § 102(b), first paragraph, for lack of enablement, has been obviated and should be withdrawn.

Although no additional fees are believed to be due at this time, the Commissioner is authorized to charge any necessary fees or other relief that may be required, or credit any overpayment to Facet Biotech Corporation, Deposit Account No. 50-4820 (**Order No. 116 US PC02**).

Respectfully submitted,

Date:

08/11/09

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Marked Up Copy of Figure 1

Figure 1

[A] VH

| | | | | | |
|---------|------------|-------------|---------------------|-------------|-----|
| | | | | <u>CDR1</u> | 40 |
| HuAIP12 | EVQLVQSGAE | VKKPGATVKI | SCKVSGYTFT | DYSMHWVRQA | |
| HuAIP13 | EVQLVQSGAE | VKKPGATVKI | SCKVSGYTFT | DYSMHWVRQA | |
| T55I | EVQLVQSGAE | VKKPGATVKI | SCKVSGYTFT | DYSMHWVRQA | |
| G104A | EVQLVQSGAE | VKKPGATVKI | SCKVSGYTFT | DYSMHWVRQA | |
| | | <u>CDR2</u> | | | 80 |
| HuAIP12 | PGKGLKWMGW | INTETGEPTY | ADDFKGRFTF | TLDTSTSTAY | |
| HuAIP13 | PGKGLKWMGW | INTETGEPTY | ADDFKGRFTF | TLDTSTSTAY | |
| | | <u>I</u> | <u>I</u> | | |
| T55I | PGKGLKWMGW | INTETGEPTY | ADDFKGRFTF | TLDTSTSTAY | |
| | | <u>I</u> | <u>I</u> | | |
| G104A | PGKGLKWMGW | INTETGEPTY | ADDFKGRFTF | TLDTSTSTAY | |
| | | <u>CDR3</u> | | | 119 |
| HuAIP12 | MELSSLRSED | TAVYYCARNY | DYDGYFDVWG | QGTTVTVSS | |
| HuAIP13 | MELSSLRSED | TAVYYCARNY | DYD <u>A</u> YFDVWG | QGTTVTVSS | |
| T55I | MELSSLRSED | TAVYYCARNY | DYDGYFDVWG | QGTTVTVSS | |
| G104A | MELSSLRSED | TAVYYCARNY | DYD <u>A</u> YFDVWG | QGTTVTVSS | |

[B] VL

| | | | | |
|---------|--------------------|-------------------------|---------------------|------------|
| | | | <u>CDR1</u> | 40 |
| HuAIP12 | DIQMTQSPSS | LSASVGRDVT | ITCKASQDIN | KYIAWYQQKP |
| HuAIP13 | DIQMTQSPSS | LSASVGRDVT | ITCKA <u>D</u> QDIN | KYIAWYQQKP |
| | | <u>CDR2</u> | | 80 |
| HuAIP12 | GKAPKLLIH | TSTLQPGIPS | RFSGSGSGRD | YTFTISSLQ |
| HuAIP13 | GKAPKLL <u>LHH</u> | TSTLQPGIPS | RFSGSGSGRD | YTFTISSLQ |
| | | <u>CDR3</u> | | 107 |
| HuAIP12 | EDIATYYCLQ | YDNL L FTFGQ | GTKLEIK | |
| HuAIP13 | EDIATYYCLQ | YD <u>S</u> LLFTFGQ | GTKLEIK | |

Alignment of the VH (A) and VL (B) amino acid sequences of HuAIP12, its derivatives (in A), and HuAIP13. The amino acid sequences of the mature VH and VL regions are shown in single letter code. Amino acids that differ from the counterparts in the HuAIP12 VH or VL are bold and double-underlined.